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**TITLE:** ANTIBACTERIAL AND FUNGICIDAL AUXILIARIES
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**ABSTRACT:**

PROBLEM TO BE SOLVED: To repress a new development of resistant bacteria based on finding of a novel effective ingredient which can be means of repressing biofilm forma tion and using the ingredient as auxiliaries for antibacterial and fungicidal agent, resulting in recovery of infected patients, complete disinfection of utensils, and promoting effective prescriptions.

SOLUTION: By finding that repression of bacterial and/or fungal formation of biofilm is possible by the use of farnesol, more preferably, by the use of farnesol with xylitol, and the above issue is possible to be resolved by providing the antibacterial and fungicidal auxiliaries containing the above compounds as effective components.

* NOTICES *



1.This document has been translated by computer. So the translation may not reflect the original precisely.
2.**** shows the word which can not be translated.
3.In the drawings, any words are not translated.

## DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[Field of the Invention]This invention is an invention about the antibacterial mildewproofing auxiliary agent which helps work of an anti-fungus and mildewproofing agent.
[0002]
[Description of the Prior Art]In recent years, explosively, the speed from which the resistant bacteria which have resistance to an antibiotic etc. appear by abuse of an antibiotic etc. is not an overstatement, although now a medical site is in a critical situation by the hospital infection according to resistant bacteria early etc.
[0003]In order to oppose to resistant bacteria, developing the new antibiotic and synthetic antimicrobials which are attacked to the element of resistant bacteria which does not yet have tolerance, or avoiding abuse of an antibiotic etc., i.e., put into practice the useless formula according to the patient's condition which is not, is mentioned.
[0004]Especially the thing for which the useless formula which is not is performed is a very effective means, in order to stop the appearance of resistant bacteria. Namely, if the antibiotic etc. which have a large antimicrobial spectrum are used preponderantly too much blindly, for example, without also fully performing specification of a disease germ or the antibiotic of various sorts is used, It is preferred to use selectively without futility the reason which will promote the appearance of the resistant bacteria to these antibiotics, and the antibiotic according to the kind of disease germ.
[0005]
[Problem(s) to be Solved by the Invention]However, even if the kind of antibiotic etc. which should be used is decided, if the antibiotic cannot contact the bacteria used as a target exactly, Since an excessive antibiotic etc. not only being used but an antibiotic etc. and bacteria will contact slowly, it may also be promoting the appearance of the resistant bacteria to the antibiotic, without being in a state with rather death-dealing bacteria. When contact inhibition states, such as such an antibiotic, continue, a patient's recovery itself is delayed and a life-threatening thing is also assumed depending on a bacterial kind or a patient's condition.
[0006]The biofilm which bacteria form is mentioned as one of the factors which bar contact with such an antibiotic etc. and bacteria. Biofilm means the film which covers the biomass surface with secrete and a precipitate, when microorganisms, such as bacteria and mold, adhere to the surface of an object or a body tissue and propagate. A biofilm formation bacillus is the formed biofilm, by barring the direct contact with an antibiotic and a biomass, resistance is shown to an antibiotic etc. and a biofilm bacillus is received, Needing an

antibiotic 1000 to 1500 times the concentration of a floating bacillus is also reported ("latest subject about Staphylococcus aureus" Japanese hide meeting magazine:109 (13), 2095-2102-1999). For this reason, compared with the case where the infectious disease by a floating bacillus is treated, it is dramatically difficult to cure the infectious disease by a biofilm formation bacillus completely. Since thorough sterilization of the biofilm formation bacillus which adhered in the medical device etc. is difficult, it is easy to become an organism of a hospital infection.

[0007]Thus, since it becomes an element very important for the infectious disease therapy of the disease germ how formation of biofilm is suppressed depending on the kind of disease germ, the restraint means of biofilm formation is examined and the result is also accepted now.

[0008]For example, a specific metallic oxide (a zinc oxide, a calcium oxide, magnesium oxide, etc.), It is traced that a hyperosmolarity, low pH (pH 5.0 or less), UV irradiation, silver, etc. control biofilm formation of a disease germ ("latest subject about Staphylococcus aureus" Japanese hide meeting magazine:109 (13), 2095-2102-1999).

[0009]However, as for biofilm, it is known that there are a variety of types and a restraint means of formation of the further biofilm continues to be desired.

[0010]Then, by the issue which this invention should solve finding out the new active principle used as the restraint means of biofilm, and using this as an auxiliary agent of an anti-fungus and mildewproofing agent, It is in controlling the new appearance of resistant bacteria by helping to base thoroughness-ization of an infectious disease patient's recovery or instrument disinfection by a biofilm formation bacillus, and to perform the useless formula which is not.

[0011]

[Problem(s) to be Solved by the Invention]The place where this invention person searched the substance which controls formation of biofilm for solution of this SUBJECT, It accepted that the biofilm depressant action for which it asks to the farnesol used for the surprising thing as antibacterial perfume from the former was accepted, and found out that it was possible to use this as an active principle of an antibacterial mildewproofing auxiliary agent, and this invention was completed.

[0012]Namely, this invention is an invention to provide the antibacterial mildewproofing auxiliary agent (henceforth this antibacterial auxiliary agent) which makes farnesol an active principle, and this antibacterial auxiliary agent, By controlling formation of the biofilm of bacteria and/or mold, it is a biofilm depressant which raises the antibacterial mildew resistant effect of an anti-fungus and mildewproofing agent.

[0013]When this invention person used as an active principle combining farnesol and xylitol, he found out that the biofilm depressant action of this antibacterial auxiliary agent improved further.

[0014]In this invention, decreasing the once formed biofilm or removing it besides controlling formation of biofilm, literally, is also included in control of biofilm.

[0015]Farnesol so that it may mention later further, It becomes possible by attacking a disease germ to remove a disease germ exactly using the antimicrobial agent which has stronger sterilizing properties of an antibiotic etc., controlling formation of biofilm for farnesol and xylitol as an active principle of this antibacterial auxiliary agent.

[0016]

[Embodiment of the Invention]Hereafter, an embodiment of the invention is described. As mentioned above, the active principle of this antibacterial auxiliary agent is farnesol (3,7,11-trimethyl 2,6,10-dodecatriene 1-oar).

Farnesol is used as antibacterial synthetic perfume (commercial item acquisition is also possible), it has the fragrance like floral one for a fresh green note, and combination to perfumery and cosmetics is accepted.
[0017]If xylitol is blended with this antibacterial auxiliary agent, the formation depressor effect of biofilm can be raised further. Though it is [ xylitol ] sugar, since it does not become a nutrient to almost all bacteria, it is used for the product in the mouth for prevention of tooth decay. It is used also as the reason which has a refreshed using feeling, and a moisturizer for cosmetics.
[0018]Since farnesol and xylitol are used widely by the above-mentioned use, they can obtain a commercial item easily and can use it in this invention. By controlling formation of the biofilm of a biofilm formation bacillus, this antibacterial auxiliary agent can weaken the resistance over the drugs by biofilm, and can raise work of an antimicrobial agent and an antifungal agent.
[0019]If this antibacterial auxiliary agent is a biofilm formation bacillus, it can make all the bacteria and mold into an applied object, but. In particular, they are a Staphylococcus (Staphiococcus) group and streptococcus (Streptococcus). Bacteria belonging to a group, For example, Staphylococcus aureus (Staphiococcus aureus), It is effective to coagulase negative Staphylococcus (coagulase-negative Staphiococci:CNS), A grouping pus chain coccus (Streptococcus pyogenes), etc. Especially, Staphylococcus aureus known as organisms by resistant bacteria (MRSA, VRSA, etc.), such as a serious hospital infection, can be made into a suitable applied object.
[0020]** As a mode of this antibacterial auxiliary agent, the mode used as disinfection auxiliary agents, such as a medical device, can be mentioned first. Once biofilm formation bacilli, such as Staphylococcus aureus, form biofilm, they have resistance to an antimicrobial agent etc., and also when just the usual disinfection of the House is insufficient, they are assumed, and a possibility that a hospital infection will occur cannot deny them, either.
[0021]Then, it is possible by processing with the usual antiseptic etc. to heighten the bactericidal effect by disinfection by leaps and bounds at the same time it controls after making this antibacterial auxiliary agent act to a medical device etc. and controlling formation of biofilm.
[0022]Although the loadings of the farnesol in this antibacterial auxiliary agent in this case can be chosen freely, its 0.001 - 10 mass % grade is usually preferred to **. Even if it is difficult to fully demonstrate sufficient biofilm depressor effect generally as it is less than 0.001 mass % and it blends exceeding 10 mass %, improvement in biofilm depressor effect corresponding to increase of loadings is not expectable.
[0023]Although the loadings of xylitol in the case of blending xylitol with this antibacterial auxiliary agent of this mode can also be chosen freely, a 0.01 - 30 mass % grade is usually preferred to **. Even if it is difficult to fully enhance the biofilm depressor effect of farnesol generally as it is less than 0.01 mass % and it blends exceeding 30 mass %, the further enhancement of the biofilm depressor effect of farnesol is not expectable.
[0024]The pharmaceutical form of this antibacterial auxiliary agent of this mode has common liquids and solutions. Namely, farnesol or farnesol, and xylitol can be dissolved, And preferably farnesol and xylitol temporally as the meltable ghost and emulsified matter using surface-active agents and amphiphile, such as the gestalt which can be saved stably, for example, an anionic detergent etc., the purpose of this invention can be attained by performing for spraying etc. this antibacterial auxiliary agent (business -- the time -- a prepared type -- good) which made farnesol and xylitol contain in the purpose part.
[0025]** Next, the mode as external preparations can be mentioned. It is accepted that it forms biofilm, expresses resistance to a therapy, it places and changes to a drug resistant bacterium when the worst, and it

becomes a very troublesome situation, a biofilm formation bacillus being fixed to a wound or a burn part, for example.

[0026]Then, it is possible by making an antimicrobial agent etc. act to bring recovery of the purpose part forward and to also control the appearance of resistant bacteria at the same time it controls after using this antibacterial auxiliary agent for the purpose part (a wound and a burn part) on the skin first and controlling formation of the biofilm in this part.

[0027]Although the loadings of the farnesol in this antibacterial auxiliary agent of this mode can be chosen freely, its 0.001 - 10 mass % grade is usually preferred to **. Even if it is difficult to fully demonstrate sufficient biofilm depressor effect generally as it is less than 0.001 mass % and it blends exceeding 10 mass %, improvement in biofilm depressor effect corresponding to increase of loadings is not expectable.

[0028]Although the loadings of xylitol in the case of blending xylitol with this antibacterial auxiliary agent of this mode can also be chosen freely, a 0.01 - 30 mass % grade is usually preferred to **. Even if it is difficult to fully enhance the biofilm depressor effect of farnesol generally as it is less than 0.01 mass % and it blends exceeding 30 mass %, the further enhancement of the biofilm depressor effect of farnesol is not expectable.

[0029]Although the amount of this antibacterial auxiliary agent used in this case can be suitably chosen according to a patient's condition, the using form of **, etc., It is preferred to use in one day or several steps so that the farnesol which is an active principle may generally be applied per day adult and about abbreviation 0.00001-0.1g may be applied to the skin. When using xylitol, it is preferred for xylitol to use so that about abbreviation 0.0001-0.3g may be applied to the skin.

[0030]The pharmaceutical form of this antibacterial auxiliary agent of this mode can choose an ointment, liquids and solutions, cream pharmaceuticals, paint, etc. as all the pharmaceutical forms which external preparations can take, and concrete targets. According to this pharmaceutical form, a publicly known base ingredient, for example, oil, a surface-active agent, higher alcohol, an antiseptic, a moisturizer, a thickener, a chelating agent, coloring matter, perfume, etc. can usually be blended with this antibacterial auxiliary agent of this mode.

[0031]** The mode as an oral administration agent can also be mentioned again. When applying external preparations, such as a case where a biofilm formation bacillus forms biofilm in the inside of the body, and the inside of a nail, forms biofilm in a difficult part, While controlling using this antibacterial auxiliary agent as an oral administration agent after controlling formation of the biofilm of these parts, by making an antimicrobial agent etc. act, it is possible to treat the infectious disease by a biofilm formation bacillus efficiently, and the appearance of resistant bacteria can also be controlled. Although the loadings of the farnesol in this antibacterial auxiliary agent in this case can be chosen freely, its 0.001 - 10 mass % grade is usually preferred to **. Even if it is difficult to fully demonstrate sufficient biofilm depressor effect generally as it is less than 0.001 mass % and it blends exceeding 10 mass %, improvement in biofilm depressor effect corresponding to increase of loadings is not expectable.

[0032]Although the loadings of xylitol in the case of blending xylitol with this antibacterial auxiliary agent of this mode can also be chosen freely, a 0.01 - 30 mass % grade is usually preferred to **. Even if it is difficult to fully enhance the biofilm depressor effect of farnesol generally as it is less than 0.01 mass % and it blends exceeding 30 mass %, the further enhancement of the biofilm depressor effect of farnesol is not expectable.

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[0034]The pharmaceutical form of this antibacterial auxiliary agent of this mode can be used as all the pharmaceutical forms which an oral administration agent can take, and concrete targets with injections, such as ** agents, such as a tablet, powders, a granule, and a pill, liquids and solutions, suspension, and an emulsion. business -- the time -- a modifier -- carrying out -- things -- being possible .

[0035]According to this pharmaceutical form, excipients, diluents, etc., such as a publicly known medicinal preparation carrier, for example, a bulking agent, an extender, a binding material, moisture adhesive material, disintegrator, and a surface-active agent, can be freely chosen as this antibacterial auxiliary agent of this mode, and can usually be blended with it.

[0036]According to that mode, the case of a suitable route of administration, for example, an injections gestalt, is medicated by intraperitoneal injection etc. intramuscular, hypodermic, and in leather in a vein, and, in the case of a ** agent gestalt, this antibacterial auxiliary agent of this oral administration agent mode may be prescribed for the patient by taking orally, enteral administration, etc.

[0037]It is possible to blend with this antibacterial auxiliary agent the drugs for attacking a pathogenic microbe and annihilating it directly, with the farnesol which is the active principle, for example, an antibiotic, synthetic antimicrobials, an antifungal agent, etc. The kind of these drugs can be chosen according to the kind of object microorganism to annihilate.

[0038]

[Example]Hereafter, although working example explains this invention still more concretely, thereby, the range of this invention is not limited.

[The example 1 of an examination] Biofilm formation inhibition test (1)

The soy bean casein digest (SCD) culture medium (made by NIHON PHARMACEUTICAL CO., LTD.) was abacterially mixed with human serum at a rate of 1:1 with the mass ratio, and 1 mL of this mixed medium was poured distributively on each 24 hole plate. Beforehand in [ after dipping 4 type collagen coating film (Celldesk: made by Sumitomo Bakelite) in these plate holes ] a SCD culture medium, The Staphylococcus aureus (Staphiococcus aureus : atopic dermatitis patient separation stock) cultivated at 37 ** for 24 hours was added so that it might become $1.0x10^8$cfu/mL. The examined substance solubilized by Tween80 0.5% after addition [Farnesol (made by DRGOCO)] was added in the plate hole so that the last concentration might be 0.2% or 0.02%. The existence of biofilm formation was visually checked after 24-hour culture at 37 **, number of microorganism was measured, and it observed with the scanning electron microscope. The result was shown in the 1st table.

[0039]

** 1 table. ----------. The number of microorganism 24 hours after biofilm formation (cfu/celldesk). ----------. Control (additive-free)+$2.9x10^8$ farnesol (0.2 %) - $4.0x10^2$ farnesol (0.02%) - $1.7x10^8$. ---------- +: -- biofilm was formed -:homeoplasia is not carried out[0040]

As a result, formation of biofilm became clear [ controlling ], although farnesol controlled growth of the bacillus by 0.2% of concentration, it became clear that biofilm was not made to form, either and growth of the bacillus was hardly influenced in 0.02% of concentration.

[0041]In Fig. 1, (1) is an electron microscope photograph (6000 times) of the Staphylococcus aureus before examined substance addition, (2) is an examined substance additive-free (control) electron microscope photograph (8000 times), and (3) is an electron microscope photograph (8000 times) of a 0.02% farnesol group. In (2), it turns out to biofilm being formed so that a biomass may be covered that formation of biofilm is not accepted by (3).

[0042][The example 2 of an examination] Biofilm formation inhibition test (2)

The soy bean casein digest (SCD) culture medium (made by NIHON PHARMACEUTICAL CO., LTD.) was abacterially mixed with human serum at a rate of 1:1 with the mass ratio, and 1 mL of this mixed medium was poured distributively on each 24 hole plate. Beforehand in [ after dipping 4 type collagen coating film (Celldesk: made by Sumitomo Bakelite) in these plate holes ] a SCD culture medium, The Staphylococcus aureus (Staphiococcus aureus JCM2151 type strain) cultivated at 37 ** for 24 hours was added so that it might become $1.0x10^8$cfu/mL. The farnesol (made by DRGOCO) solubilized by Tween80 0.5% after addition so that the last concentration may be 0.2%, When xylitol (made by Kalter hood Saiensu-Sha) was added, the xylitol 50% solution which sterilized beforehand was added in the plate hole so that the last concentration might be 5%. The existence of biofilm formation was visually checked after 72-hour culture at 37 **, number of microorganism was measured, and it observed with the scanning electron microscope. The result was shown in the 2nd table.

[0043]

** 2 table. ----------. The number of microorganism 72 hours after biofilm formation (cfu/celldesk). ---------- ---------- control (additive-free) + $3.2x10^9$ farnesol (0.2 %) ** $2.2x10^4$ farnesol (0.02%)

+ xylitol (5%) - $1.2x10^4$---------- +: -- **: in which biofilm was formed -- said -- it is not formed most -:homeoplasia is not carried out[0044]As a result, control growth of a bacillus by adding farnesol by 0.2% of the last concentration also in culture for 72 hours, and. The operation which controls formation of biofilm was accepted and it became clear further by adding combining xylitol to farnesol that biofilm formation depressor effect is enhanced remarkably.

[0045]In Fig. 2, (1) is an electron microscope photograph (6000 times) of the Staphylococcus aureus before examined substance addition, and (2), In an examined substance additive-free (control) electron microscope photograph (6000 times), (3) is an electron microscope photograph (6000 times) of a 0.2% farnesol group, and (4) is an electron microscope photograph (6000 times) of a 0.2% farnesol+5% xylitol group. Like above-mentioned Fig. 1, in (2), biofilm was formed so that a biomass might be covered. On the other hand, formation of biofilm is controlled and it turns out (3) by (4) that the formation of biofilm itself is not accepted.

[0046][The example 3 of an examination] The SCD culture medium was abacterially mixed with biofilm removal examination human serum at a rate of 1:1 with the mass ratio, and 1 mL of this mixed medium was poured distributively on each 24 hole plate. Beforehand in [ after dipping 4 type collagen coating film (Celldesk: made by Sumitomo Bakelite) in these plate holes ] a SCD culture medium, The Staphylococcus aureus (Staphiococcus aureus : atopic dermatitis patient separation stock) cultivated at 37 ** for 24 hours was added so that it might become $1.0x10^8$cfu/mL. The examined substance which performed culture at 37 ** after addition for 24 hours, checked the biofilm formation in each plate hole, and was solubilized by Tween80 0.5% to this [Farnesol (DRGOCO)] was added in the plate hole so that the last concentration might be 0.2% or

0.02%. The existence of biofilm formation was visually checked after 72-hour culture at 37 **, number of microorganism was measured, and it observed with the scanning electron microscope. The result was shown in the 3rd table.

[0047]

** 3 table. ----------. The number of microorganism 72 hours after biofilm formation (cfu/celldesk). ----------. Control (additive-free) + $1.5x10^9$ farnesol (0.2 %) - $9.0x10^2$ farnesol (0.02%) - $5.2x10^8$. ---------- +: -- biofilm was formed -:homeoplasia is not carried out[0048] As a result, even if farnesol was after biofilm formation at 0.2%, it became clear that a bacillus is sterilized, biofilm is extinguished, and biofilm might be extinguished although growth of a bacillus is not affected in 0.02%.

[0049]From the result of these examples of an examination, farnesol, Even if it was the low concentration which is less than Media Interface Connector, it became clear that it was possible to extinguish the biofilm which controlled generating of the biofilm of a biofilm formation bacillus, and was once generated, and it was possible to also use small-quantity combination as an active principle of an antibacterial auxiliary agent. It became clear by using combining farnesol and xylitol for the above-mentioned biofilm formation depressant action to be enhanced remarkably.

[0050]

[Effect of the Invention]By this invention, the efficiency of work of an antimicrobial agent etc. is increased by controlling formation of the biofilm of a biofilm formation bacillus, and the antibacterial mildewproofing auxiliary agent which can also control generating of resistant bacteria is provided further.

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[Translation done.]